Improved description of complex plasticity and interactions in protein-ligand simulations

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Bibliography

[1] R. B. Silverman and M. W. Holladay, *The organic chemistry of drug design and drug action*. Academic press, 2014.

[2] R. E. Babine and S. L. Bender, "Molecular recognition of protein-ligand complexes: applications to drug design," *Chemical reviews*, vol. 97, no. 5, pp. 1359–1472, 1997.

[3] G. C. Terstappen and A. Reggiani, "*In silico* research in drug discovery," *Trends Pharmacol. Sci.*, vol. 22, no. 1, pp. 23–26, 2001.

[4] M. Karplus and J. A. McCammon, "Molecular dynamics simulations of biomolecules," *Nat. Struct. Mol. Biol.*, vol. 9, no. 9, pp. 646–652, 2002.

[5] M. P. Jacobson, G. A. Kaminski, R. A. Friesner, and C. S. Rapp, "Force field validation using protein side chain prediction," *J. Phys. Chem. B*, vol. 106, no. 44, pp. 11673–11680, 2002.

[6] G. J. Rocklin, D. L. Mobley, and K. A. Dill, "Calculating the sensitivity and robustness of binding free energy calculations to force field parameters," *J. Chem. Theory Comput.*, vol. 9, no. 7, pp. 3072–3083, 2013.

[7] J. W. Ponder and D. A. Case, "Force fields for protein simulations," *Adv. Protein Chem.*, vol. 66, pp. 27–86, 2003.

[8] M. Levitt and A. Warshel, "Computer simulation of protein folding," *Nature*, vol. 253, no. 5494, pp. 694–698, 1975.

[9] C. D. Snow, H. Nguyen, V. S. Pande, and M. Gruebele, "Absolute comparison of simulated and experimental protein-folding dynamics," *Nature*, vol. 420, no. 6911, pp. 102–106, 2002.

[10] W. F. van Gunsteren, D. Bakowies, R. Baron, I. Chandrasekhar, M. Christen, X. Daura, P. Gee, D. P. Geerke, A. Glaettli, P. H. Huenenberger, M. A. Kastenholz, C. Ostenbrink, M. Schenk, D. Trzesniak, N. F. A. van der Vegt, and H. B. Yu, "Biomolecular modeling: Goals, problems, perspectives," *Angew. Chem., Int. Ed.*, vol. 45, no. 25, pp. 4064–4092, 2006.

[11] Y. Shan, E. T. Kim, M. P. Eastwood, R. O. Dror, M. A. Seeliger, and D. E. Shaw, "How does a drug molecule find its target binding site?," *J. Am. Chem. Soc.*, vol. 133, no. 24, pp. 9181–9183, 2011.

[12] K. A. Dill and J. L. MacCallum, "The protein-folding problem, 50 years on," *Science*, vol. 338, no. 6110, pp. 1042–1046, 2012.

[13] R. O. Dror, R. M. Dirks, J. Grossman, H. Xu, and D. E. Shaw, "Biomolecular simulation: a computational microscope for molecular biology," *Ann. Rev. Biophys*, vol. 41, pp. 429–452, 2012.

[14] D. W. Borhani and D. E. Shaw, "The future of molecular dynamics simulations in drug discovery," *J. Comput. Aided Mol. Des.*, vol. 26, no. 1, pp. 15–26, 2012.

[15] A. Rahman, "Correlations in the motion of atoms in liquid argon," *Phys. Rev.*, vol. 136, pp. A405–A411, 1964.

[16] R. O. Dror, M. Jensen, D. W. Borhani, and D. E. Shaw, "Exploring atomic resolution physiology on a femtosecond to millisecond timescale using molecular dynamics simulations," *J. Gen. Physiol.*, vol. 135, no. 6, pp. 555–562, 2010.

[17] L. Miao and K. Schulten, "Probing a structural model of the nuclear pore complex channel through molecular dynamics," *Biophys. J.*, vol. 98, no. 8, pp. 1658–1667, 2010.

[18] D. E. Shaw, "166 millisecond-long molecular dynamics simulations of proteins on a special-purpose machine," *J. Biomolec. Struct. Dyn.*, vol. 31, pp. 108–108, 2013.

[19] D.-A. Silva, D. R. Weiss, F. P. Avila, L.-T. Da, M. Levitt, D. Wang, and X. Huang, "Millisecond dynamics of RNA polymerase II translocation at atomic resolution," *Proc. Natl. Acad. Sci.*, vol. 111, no. 21, pp. 7665–7670, 2014.

[20] H. J. Berendsen, *Simulating the physical world: hierarchical modeling from quantum mechanics to fluid dynamics*. Cambridge University Press, 2007.

[21] W. D. Cornell, P. Cieplak, C. I. Bayly, I. R. Gould, K. M. Merz, D. M. Ferguson, D. C. Spellmeyer, T. Fox, J. W. Caldwell, and P. A. Kollman, "A second generation force field for the simulation of proteins, nucleic acids, and organic molecules," *J. Am. Chem. Soc.*, vol. 117, no. 19, pp. 5179–5197, 1995.

[22] W. L. Jorgensen, D. S. Maxwell, and J. Tirado-Rives, "Development and testing of the OPLS all-atom force field on conformational energetics and properties of organic liquids," *J. Am. Chem. Soc.*, vol. 118, no. 45, pp. 11225–11236, 1996.

[23] A. D. MacKerell, D. Bashford, M. Bellott, R. L. Dunbrack, J. D. Evanseck, M. J. Field, S. Fischer, J. Gao, H. Guo, S. Ha, D. Joseph-McCarthy, L. Kuchnir, K. Kuczera, F. Lau, C. Mattos, S. Michnick, T. Ngo, D. T. Nguyen, B. Prodhom, W. E. Reiher, B. Roux, M. Schlenkrich, J. C. Smith, R. Stote, J. Straub, M. Watanabe, J. Wiorkiewicz-Kuczera, D. Yin, and M. Karplus, "All-atom empirical potential for molecular modeling and dynamics studies of proteins," *J. Phys. Chem. B*, vol. 102, no. 18, pp. 3586–3616, 1998.

[24] C. Oostenbrink, A. Villa, A. E. Mark, and W. F. van Gunsteren, "A biomolecular force field based on the free enthalpy of hydration and solvation: The GROMOS force-field parameter sets 53A5 and 53A6," *J. Comput. Chem.*, vol. 25, no. 13, pp. 1656–1676, 2004.

[25] D. P. Geerke and W. F. van Gunsteren, "Calculation of the free energy of polarization: Quantifying the effect of explicitly treating electronic polarization on the transferability of force-field parameters," *J. Phys. Chem. B*, vol. 111, no. 23, pp. 6425–6436, 2007.

[26] H. B. Yu and W. F. van Gunsteren, "Accounting for polarization in molecular simulation," *Comput. Phys. Commun.*, vol. 172, no. 2, pp. 69–85, 2005.

[27] A. K. Rappé and W. A. Goddard, "Charge equilibration for molecular-dynamics simulations," *J. Phys. Chem.*, vol. 95, no. 8, pp. 3358–3363, 1991.

[28] S. W. Rick, S. J. Stuart, and B. J. Berne, "Dynamical fluctuating charge force-fields - application to liquid water," *J. Chem. Phys.*, vol. 101, no. 7, pp. 6141–6156, 1994.

[29] A. Warshel and M. Levitt, "Theoretical studies of enzymic reactions - dielectric, electrostatic and steric stabilization of carbonium-ion in reaction of lysozyme," *J. Mol. Biol.*, vol. 103, no. 2, pp. 227–249, 1976.

[30] F. Vesely, "N-particle dynamics of polarizable stockmayer-type molecules," *J. Comput. Phys.*, vol. 24, no. 4, pp. 361–371, 1977.

[31] D. van Belle, I. Couplet, M. Prevost, and S. J. Wodak, "Calculations of electrostatic properties in proteins - Analysis of contributions from induced protein dipoles," *J. Mol. Biol.*, vol. 198, no. 4, pp. 721–735, 1987.

[32] P. Drude, *The theory of optics*. Longmans, Green and CO.: New York, 1902.

[33] T. P. Straatsma and J. A. McCammon, "Molecular dynamics simulations with interaction potentials including polarization development of a non-iterative method and application to water," *Mol. Simul.*, vol. 5, no. 3-4, pp. 181–192, 1990.

[34] J. W. Caldwell, L. X. Dang, and P. A. Kollman, "Implementation of nonadditive intermolecular potentials by use of molecular-dynamics - development of a water water potential and water ion cluster interactions," *J. Am. Chem. Soc.*, vol. 112, no. 25, pp. 9144–9147, 1990.

[35] H. B. Yu, T. Hansson, and W. F. van Gunsteren, "Development of a simple, self-consistent polarizable model for liquid water," *J. Chem. Phys.*, vol. 118, no. 1, pp. 221–234, 2003.

[36] M. Sprik, "Hydrogen-bonding and the static dielectric-constant in liquid water," *J. Chem. Phys.*, vol. 95, no. 9, pp. 6762–6769, 1991.

[37] D. van Belle, M. Froeyen, G. Lippens, and S. Wodak, "Molecular-dynamics simulation of polarizable water by extended Lagrangian method," *Mol. Phys.*, vol. 77, no. 2, pp. 239–255, 1992.

[38] D. van Belle and S. J. Wodak, "Extended Lagrangian-formalism applied to temperature control and electronic polarization effects in molecular-dynamics simulations," *Comput. Phys. Commun.*, vol. 91, no. 1-3, pp. 253–262, 1995.

[39] K. Miller, "Calculation of the molecular polarizability tensor," *J. Am. Chem. Soc.*, vol. 112, no. 23, pp. 8543–8551, 1990.

[40] J. Applequist, J. R. Carl, and K. K. Fung, "Atom dipole interaction-model for molecular polarizability - application to polyatomic molecules - and determination of atom polarizabilities," *J. Am. Chem. Soc.*, vol. 94, no. 9, pp. 2952–2960, 1972.

[41] S. Rick and S. Stuart, *Potentials and algorithms for incorporating polarizability in computer simulations*, vol. 18. John Wiley & Sons, Inc., New Jersey, USA, 2002.

[42] B. Thole, "Molecular polarizabilities calculated with a modified dipole interaction," *Chem. Phys.*, vol. 59, no. 3, pp. 341–350, 1981.

[43] A. Kunz and W. F. Van Gunsteren, "Development of a nonlinear classical polarization model for liquid water and aqueous solutions: COS/D," *J. Phys. Chem. A*, vol. 113, no. 43, pp. 11570–11579, 2009.

[44] V. M. Anisimov, G. Lamoureux, I. V. Vorobyov, N. Huang, B. Roux, and A. D. MacKerell, "Determination of electrostatic parameters for a

polarizable force field based on the classical Drude oscillator," *J. Chem. Theory Comput.*, vol. 1, no. 1, pp. 153–168, 2005.

[45] G. Lamoureux, A. D. MacKerell, and B. Roux, "A simple polarizable model of water based on classical Drude oscillators," *J. Chem. Phys.*, vol. 119, no. 10, pp. 5185–5197, 2003.

[46] D. P. Geerke and W. F. van Gunsteren, "The performance of non-polarizable and polarizable force-field parameter sets for ethylene glycol in molecular dynamics simulations of the pure liquid and its aqueous mixtures," *Mol. Phys.*, vol. 105, no. 13-14, pp. 1861–1881, 2007.

[47] V. M. Anisimov, I. V. Vorobyov, B. Roux, and A. D. MacKerell, "Polarizable empirical force field for the primary and secondary alcohol series based on the classical Drude model," *J. Chem. Theory Comput.*, vol. 3, no. 6, pp. 1927–1946, 2007.

[48] J. W. Caldwell and P. A. Kollman, "Structure and properties of neat liquids using nonadditive molecular-dynamics - water, methanol, and n-methylacetamide," *J. Phys. Chem.*, vol. 99, no. 16, pp. 6208–6219, 1995.

[49] J. L. Gao, D. Habibollazadeh, and L. Shao, "A polarizable intermolecular potential function for simulation of liquid alcohols," *J. Phys. Chem.*, vol. 99, no. 44, pp. 16460–16467, 1995.

[50] L. X. Dang and T. M. Chang, "Many-body interactions in liquid methanol and its liquid/vapor interface: A molecular dynamics study," *J. Chem. Phys.*, vol. 119, no. 18, pp. 9851–9857, 2003.

[51] S. Patel and C. L. Brooks, "A nonadditive methanol force field: Bulk liquid and liquid-vapor interfacial properties via molecular dynamics simulations using a fluctuating charge model," *J. Chem. Phys.*, vol. 122, no. 2, p. 024508, 2005.

[52] J. E. Jones, "On the determination of molecular fields. II. From the equation of state of a gas," *Proc. R. Soc. A*, vol. 106, no. 738, pp. 463–477, 1924.

[53] A. K. Malde, L. Zuo, M. Breeze, M. Stroet, D. Poger, P. C. Nair, C. Oostenbrink, and A. E. Mark, "An Automated Force Field Topology Builder (ATB) and repository: version 1.0," *J. Chem. Theory Comput.*, vol. 7, no. 12, pp. 4026–4037, 2011.

[54] G. Zhou, R. Cummings, Y. Li, S. Mitra, H. Wilkinson, A. Elbrecht, J. Hermes, J. Schaeffer, R. Smith, and D. Moller, "Nuclear receptors have distinct affinities for coactivators: Characterization by fluorescence resonance energy transfer," *Mol. Endocrinol.*, vol. 12, no. 10, pp. 1594–1604, 1998.

[55] A. M. Brzozowski, A. C. W. Pike, Z. Dauter, R. E. Hubbard, T. Bonn, O. Engstrom, L. Ohman, G. L. Greene, J.-A. Gustafsson, and M. Carlquist, "Molecular basis of agonism and antagonism in the oestrogen receptor," *Nature*, vol. 389, no. 6652, pp. 753–758, 1997.

[56] O. P. J. van Linden, A. J. Kooistra, R. Leurs, I. J. P. de Esch, and C. de Graaf, "KLIFS: a knowledge-based structural database to navigate Kinase–Ligand Interaction Space," *J. Med. Chem.*, vol. 57, no. 2, pp. 249–277, 2014.

[57] A. Kooistra, C. de Graaf, and H. Timmerman, "The receptor concept in 3D: from hypothesis and metaphor to GPCR–ligand structures," *Neurochem. Res.*, pp. 1–12, 2014.

[58] B. Green, T. Monger, R. Alfano, B. Aton, and R. Callender, "Cis-trans isomerisation in rhodopsin occurs in picoseconds," *Nature*, vol. 269, no. 5624, pp. 179–180, 1977.

[59] M. Akke, "NMR methods for characterizing microsecond to millisecond dynamics in recognition and catalysis," *Curr. Opin. Struct. Biol.*, vol. 12, no. 5, pp. 642–647, 2002.

[60] J. L. Klepeis, K. Lindorff-Larsen, R. O. Dror, and D. E. Shaw, "Long-timescale molecular dynamics simulations of protein structure and function," *Curr. Opin. Struct. Biol.*, vol. 19, no. 2, pp. 120 – 127, 2009.

[61] C. Oostenbrink, A. de Ruiter, J. Hritz, and N. P. E. Vermeulen, "Malleability and versatility of cytochrome P450 active sites studied by molecular simulations.," *Curr. Drug Metab.*, vol. 13, no. 2, pp. 190–196, 2012.

[62] H. Kokubo, T. Tanaka, and Y. Okamoto, "Prediction of pprotein–ligand binding structures by replica-exchange umbrella sampling simulations: Application to kinase systems," *J. Chem. Theory Comput.*, vol. 9, no. 10, pp. 4660–4671, 2013.

[63] T. Huber, A. Torda, and W. F. van Gunsteren, "Local elevation: A method for improving the searching properties of molecular dynamics simulation," *J. Comput. Aided Mol. Des.*, vol. 8, no. 6, pp. 695–708, 1994.

[64] Y. Okamoto, "Generalized-ensemble algorithms: enhanced sampling techniques for Monte Carlo and molecular dynamics simulations," *J. Molec. Graph. Model.*, vol. 22, no. 5, pp. 425–439, 2004.

[65] S. Kirkpatrick, C. D. Gelatt, and M. P. Vecchi, "Optimization by simulated annealing," *Science*, vol. 220, no. 4598, pp. 671–680, 1983.

[66] P. C. Nair, A. K. Malde, N. Drinkwater, and A. E. Mark, "Missing fragments: Detecting cooperative binding in fragment-based drug design," *ACS Med. Chem. Lett.*, vol. 3, no. 4, pp. 322–326, 2012.

[67] K. Wang, J. D. Chodera, Y. Yang, and M. R. Shirts, "Identifying ligand binding sites and poses using GPU-accelerated Hamiltonian replica exchange molecular dynamics," *J. Comput. Aided Mol. Des.*, vol. 27, no. 12, pp. 989–1007, 2013.

[68] A. K. Malde and A. E. Mark, "Challenges in the determination of the binding modes of non-standard ligands in X-ray crystal complexes," *J. Comput. Aided Mol. Des.*, vol. 25, no. 1, pp. 1–12, 2011.

[69] M. C. Damsten, J. N. M. Commandeur, A. Fidder, A. G. Hulst, D. Touw, D. Noort, and N. P. E. Vermeulen, "Liquid chromatography/tandem mass spectrometry detection of covalent binding of acetaminophen to human serum albumin," *Drug Metab. Dispos.*, vol. 35, no. 8, pp. 1408–1417, 2007.

[70] M. C. Damsten, B. M. van Vugt-Lussenburg, T. Zeldenthuis, J. S. de Vlieger, J. N. Commandeur, and N. P. E. Vermeulen, "Application of drug metabolising mutants of cytochrome P450 BM3 (CYP102A1) as biocatalysts for the generation of reactive metabolites," *Chem.-Biol. Interact.*, vol. 171, no. 1, pp. 96 – 107, 2008.

[71] H. Venkataraman, S. B. de Beer, D. P. Geerke, N. P. E. Vermeulen, and J. N. M. Commandeur, "Regio- and stereoselective hydroxylation of optically active α-ionone enantiomers by engineered Cytochrome P450 BM3 mutants," *Adv. Synth. Catal.*, vol. 354, no. 11-12, pp. 2172–2184, 2012.

[72] S. B. A. de Beer, L. A. H. van Bergen, K. Keijzer, V. Rea, H. Venkataraman, C. Fonseca Guerra, F. Matthias Bickelhaupt, N. P. E. Vermeulen, J. N. M. Commandeur, and D. P. Geerke, "The role of protein plasticity in computational rationalization studies on regioselectivity in testosterone hydroxylation by Cytochrome P450 BM3 mutants," *Curr. Drug Metab.*, vol. 13, no. 2, pp. 155–166, 2012.

[73] S. B. A. de Beer, H. Venkataraman, D. P. Geerke, C. Oostenbrink, and N. P. Vermeulen, "Free energy calculations give insight into the stereoselective hydroxylation of α-ionones by engineered Cytochrome P450 BM3 mutants," *J. Chem. Inf. Model.*, vol. 52, no. 8, pp. 2139–2148, 2012.

[74] J. Åqvist and C. Medina, "A new method for predicting binding affinity in computer-aided drug design," *Protein Eng.*, vol. 7, no. 3, pp. 385–391, 1994.

[75] E. Stjernschantz and C. Oostenbrink, "Improved ligand-protein binding affinity predictions using multiple binding modes," *Biophys. J.*, vol. 98, no. 11, pp. 2682–2691, 2010.

[76] L. Perić-Hassler, E. Stjernschantz, C. Oostenbrink, and D. P. Geerke, "CYP 2D6 binding affinity predictions using multiple ligand and protein conformations," *Int. J. Mol. Sci.*, vol. 14, no. 12, pp. 24514–24530, 2013.

[77] G. E. Moore, "Cramming more components onto integrated circuits, reprinted from electronics, volume 38, number 8, april 19, 1965, pp.114 ff.," *J. Solid-State Circuits IEEE*, vol. 11, no. 5, pp. 33–35, 2006.

[78] T. A. Wassenaar, M. van Dijk, N. Loureiro-Ferreira, G. van der Schot, S. J. de Vries, C. Schmitz, J. van der Zwan, R. Boelens, A. Giachetti, L. Ferella, A. Rosato, I. Bertini, T. Herrmann, H. R. Jonker, A. Bagaria, V. Jaravine, P. Güntert, H. Schwalbe, W. F. Vranken, J. F. Doreleijers, G. Vriend, G. W. Vuister, D. Franke, A. Kikhney, D. I. Svergun, R. H. Fogh, J. Ionides, E. D. Laue, C. Spronk, S. Jurkša, M. Verlato, S. Badoer, S. Dal Pra, M. Mazzucato, E. Frizziero, and A. M. Bonvin, "WeNMR: Structural biology on the grid," *J. Grid Comp.*, vol. 10, no. 4, pp. 743–767, 2012.

[79] D. E. Shaw, M. M. Deneroff, R. O. Dror, J. S. Kuskin, R. H. Larson, J. K. Salmon, C. Young, B. Batson, K. J. Bowers, J. C. Chao, M. P. Eastwood, J. Gagliardo, J. P. Grossman, C. R. Ho, D. J. Ierardi, I. Kolossváry, J. L. Klepeis, T. Layman, C. McLeavey, M. A. Moraes, R. Mueller, E. C. Priest, Y. Shan, J. Spengler, M. Theobald, B. Towles, and S. C. Wang, "Anton, a special-purpose machine for molecular dynamics simulation," *SIGARCH Comput. Archit. News*, vol. 35, no. 2, pp. 1–12, 2007.

[80] J. Owens, M. Houston, D. Luebke, S. Green, J. Stone, and J. Phillips, "GPU computing," *Proc.e IEEE*, vol. 96, no. 5, pp. 879–899, 2008.

[81] X. Jin, L. Zhao, and J. Yang, "A CUDA based solute interaction calcula-

tion of biomolecular simulation for GROMOS," in *Computer Science and Network Technology (ICCSNT), 2011 International Conference on*, vol. 2, pp. 820–824, 2011.

[82] N. Schmid, M. Bötschi, and W. F. van Gunsteren, "A GPU solvent–solvent interaction calculation accelerator for biomolecular simulations using the GROMOS software," *J. Comput. Chem.*, vol. 31, no. 8, pp. 1636–1643, 2010.

[83] W. Liu, B. Schmidt, G. Voss, and W. Müller-Wittig, "Molecular dynamics simulations on commodity GPUs with CUDA," in *High Performance Computing – HiPC 2007* (S. Aluru, M. Parashar, R. Badrinath, and V. Prasanna, eds.), vol. 4873 of *Lecture Notes in Computer Science*, pp. 185–196, Springer Berlin Heidelberg, 2007.

[84] M. Shirts and V. Pande, "Computing - Screen savers of the world unite!," *Science*, vol. 290, no. 5498, pp. 1903–1904, 2000.

[85] V. S. Pande, I. Baker, J. Chapman, S. P. Elmer, S. Khaliq, S. M. Larson, Y. M. Rhee, M. R. Shirts, C. D. Snow, E. J. Sorin, and B. Zagrovic, "Atomistic protein folding simulations on the submillisecond time scale using worldwide distributed computing," *Biopolymers*, vol. 68, no. 1, pp. 91–109, 2003.

[86] A. Patriksson and D. van der Spoel, "A temperature predictor for parallel tempering simulations," *Phys. Chem. Chem. Phys.*, vol. 10, pp. 2073–2077, 2008.

[87] P. Rydberg, M. Rostkowski, D. E. Gloriam, and L. Olsen, "The contribution of atom accessibility to site of metabolism models for Cytochromes P450," *Mol. Pharm.*, vol. 10, no. 4, pp. 1216–1223, 2013.

[88] T. Steger-Hartmann, F. Pognan, F. Sanz, and C. A. Diaz, "*In silico* prediction of in vivo toxicities (eTox)—The Innovative Medicines Initiative Approach," *Toxicol Lett.*, vol. 189, p. S258, 2009.

[89] N. Schmid, C. D. Christ, M. Christen, A. P. Eichenberger, and W. F. Van Gunsteren, "Architecture, implementation and parallelisation of the GROMOS software for biomolecular simulation," *Comput. Phys. Commun.*, vol. 183, no. 4, pp. 890–903, 2012.

[90] B. Hess, C. Kutzner, D. van der Spoel, and E. Lindahl, "GROMACS 4: Algorithms for highly efficient, load-balanced, and scalable molecular simulation," *J. Chem. Theory Comput.*, vol. 4, no. 3, pp. 435–447, 2008.

[91] D. Frenkel and B. Smit, *Understanding molecular simulation.* Elsevier: San Diego, 2002.

[92] V. A. Voelz, G. R. Bowman, K. Beauchamp, and V. S. Pande, "Molecular simulation of ab initio protein folding for a millisecond folder NTL9(1-39)," *J. Am. Chem. Soc.*, vol. 132, no. 5, pp. 1526–1528, 2010.

[93] R. O. Dror, D. H. Arlow, P. Maragakis, T. J. Mildorf, A. C. Pan, H. Xu, D. W. Borhani, and D. E. Shaw, "Activation mechanism of the beta(2)-adrenergic receptor," *Proc. Natl. Acad. Sci. U. S. A.*, vol. 108, no. 46, pp. 18684–18689, 2011.

[94] P. H. Hünenberger and W. F. van Gunsteren, *Computer simulation of biomolecular systems, theoretical and experimental applications*, vol. 3.

Kluwer academic publisher, Dordrecht, the Netherlands, 1997.

[95] A. D. MacKerell, "Empirical force fields for biological macromolecules: Overview and issues," *J. Comput. Chem.*, vol. 25, no. 13, pp. 1584–1604, 2004.

[96] J. Wang, R. Wolf, J. Caldwell, P. Kollman, and D. Case, "Development and testing of a general amber force field," *J. Comput. Chem.*, vol. 25, no. 9, pp. 1157–1174, 2004.

[97] L. J. Yang, C. H. Tan, M. J. Hsieh, J. M. Wang, Y. Duan, P. Cieplak, J. Caldwell, P. A. Kollman, and R. Luo, "New-generation amber united-atom force field," *J. Phys. Chem. B*, vol. 110, no. 26, pp. 13166–13176, 2006.

[98] A. D. MacKerell, N. Banavali, and N. Foloppe, "Development and current status of the CHARMM force field for nucleic acids," *Biopolymers*, vol. 56, no. 4, pp. 257–265, 2000.

[99] K. Vanommeslaeghe, E. Hatcher, C. Acharya, S. Kundu, S. Zhong, J. Shim, E. Darian, O. Guvench, P. Lopes, I. Vorobyov, and A. D. MacKerell, "CHARMM general force field: A force field for drug-like molecules compatible with the CHARMM all-atom additive biological force fields," *J. Comput. Chem.*, vol. 31, no. 4, pp. 671–690, 2010.

[100] W. L. Jorgensen and J. Tirado-Rives, "The OPLS [optimized potentials for liquid simulations] potential functions for proteins, energy minimizations for crystals of cyclic peptides and crambin," *J. Am. Chem. Soc.*, vol. 110, no. 6, pp. 1657–1666, 1988.

[101] G. A. Kaminski, R. A. Friesner, J. Tirado-Rives, and W. L. Jorgensen, "Evaluation and reparametrization of the OPLS-AA force field for proteins via comparison with accurate quantum chemical calculations on peptides," *J. Phys. Chem. B*, vol. 105, no. 28, pp. 6474–6487, 2001.

[102] W. F. van Gunsteren, S. R. Billeter, A. A. Eising, P. H. Hünenberger, P. Krüger, A. E. Mark, W. R. P. Scott, and I. G. Tironi, *Biomolecular simulation: The GROMOS96 manual and user guide.* vdf Hochschulverlag, ETH Zurich, Switzerland, 1996.

[103] N. Schmid, A. P. Eichenberger, A. Choutko, S. Riniker, M. Winger, A. E. Mark, and W. F. van Gunsteren, "Definition and testing of the GROMOS force-field versions 54A7 and 54B7," *Eur. Biophys. J.*, vol. 40, no. 7, pp. 843–856, 2011.

[104] P. J. van Maaren and D. van der Spoel, "Molecular dynamics simulations of water with novel shell-model potentials," *J. Phys. Chem. B*, vol. 105, no. 13, pp. 2618–2626, 2001.

[105] E. Harder, V. M. Anisimov, T. W. Whitfield, A. D. MacKerell, and B. Roux, "Understanding the dielectric properties of liquid amides from a polarizable force field," *J. Phys. Chem. B*, vol. 112, no. 11, pp. 3509–3521, 2008.

[106] G. Lamoureux and B. Roux, "Modeling induced polarization with classical Drude oscillators: Theory and molecular dynamics simulation algorithm," *J. Chem. Phys.*, vol. 119, no. 6, pp. 3025–3039, 2003.

[107] D. P. Fernández, Y. Mulev, A. R. H. Goodwin, and J. M. H. Levelt Sengers, "A database for the static dielectric constant of water and steam," *J. Phys.*

Chem., vol. 24, no. 1, pp. 33–70, 1995.
[108] L. Dang, "The nonadditive intermolecular potential for water revised," *J. Chem. Phys.*, vol. 97, no. 4, pp. 2659–2660, 1992.
[109] D. Smith and L. Dang, "Computer simulations of nacl association in polarizable water," *J. Chem. Phys.*, vol. 100, no. 5, pp. 3757–3766, 1994.
[110] H. Stern, F. Rittner, B. Berne, and R. Friesner, "Combined fluctuating charge and polarizable dipole models: Application to a five-site water potential function," *J. Chem. Phys.*, vol. 115, no. 5, pp. 2237–2251, 2001.
[111] G. Lamoureux, E. Harder, I. V. Vorobyov, B. Roux, and A. D. MacKerell, "A polarizable model of water for molecular dynamics simulations of biomolecules," *Chem. Phys. Lett.*, vol. 418, no. 1-3, pp. 245–249, 2006.
[112] H. B. Yu and W. F. van Gunsteren, "Charge-on-spring polarizable water models revisited: From water clusters to liquid water to ice," *J. Chem. Phys.*, vol. 121, no. 19, pp. 9549–9564, 2004.
[113] D. R. Lide, *CRC Handbook of chemistry and physics*. CRC Press, 2007.
[114] H. B. Yu, D. P. Geerke, H. Y. Liu, and W. F. van Gunsteren, "Molecular dynamics simulations of liquid methanol and methanol-water mixtures with polarizable models," *J. Comput. Chem.*, vol. 27, no. 13, pp. 1494–1504, 2006.
[115] B. Schropp and P. Tavan, "The polarizability of point-polarizable water models: Density functional theory molecular mechanics results," *J. Phys. Chem. B*, vol. 112, no. 19, pp. 6233–6240, 2008.
[116] P. Y. Ren and J. W. Ponder, "Consistent treatment of inter- and intramolecular polarization in molecular mechanics calculations," *J. Comput. Chem.*, vol. 23, no. 16, pp. 1497–1506, 2002.
[117] P. Y. Ren, C. Wu, and J. W. Ponder, "Polarizable atomic multipole-based molecular mechanics for organic molecules," *J. Chem. Theory Comput.*, vol. 7, no. 10, pp. 3143–3161, 2011.
[118] C. M. Baker and A. D. MacKerell, "Polarizability rescaling and atom-based Thole scaling in the CHARMM Drude polarizable force field for ethers," *J. Mol. Model.*, vol. 16, no. 3, pp. 567–576, 2010.
[119] A. D. Becke, "Density-functional thermochemistry. 3. the role of exact exchange," *J. Chem. Phys.*, vol. 98, no. 7, pp. 5648–5652, 1993.
[120] P. J. Stephens, F. J. Devlin, C. F. Cabalowski, and M. J. Frisch, "Ab-initio calculation of vibrational absorption and circular-dichroism spectra using density-functional force-fields," *J. Phys. Chem.*, vol. 98, no. 45, pp. 11623–11627, 1994.
[121] R. H. Hertwig and W. Koch, "On the parameterization of the local correlation functional. What is Becke-3-LYP?," *Chem. Phys. Lett.*, vol. 268, no. 5-6, pp. 345–351, 1997.
[122] R. A. Kendall, T. H. Dunning, and R. J. Harrison, "Electron-affinities of the 1s-row atoms revisited - systematic basis-sets and wave-functions," *J. Chem. Phys.*, vol. 96, no. 9, pp. 6796–6806, 1992.
[123] M. W. Schmidt, K. K. Baldridge, J. A. Boatz, S. T. Elbert, M. S. Gordon, J. H. Jensen, S. Koseki, N. Matsunaga, K. A. Nguyen, S. J. Su, T. L. Windus, M. Dupuis, and J. A. Montgomery, "General atomic and molecular

electronic-structure system," *J. Comput. Chem.*, vol. 14, no. 11, pp. 1347–1363, 1993.

[124] M. Gordon and M. Schmidt, *Theory and applications of computational chemistry: the first forty years*. Amsterdam: Elsevier, 2005.

[125] H. J. C. Berendsen, J. P. M. Postma, W. F. van Gunsteren, and J. Hermans, *Intermolecular forces*. Reidel, Dordrecht, The Netherlands, 1981.

[126] H. J. C. Berendsen, J. R. Grigera, and T. P. Straatsma, "The missing term in effective pair potentials," *J. Phys. Chem.*, vol. 91, no. 24, pp. 6269–6271, 1987.

[127] R. Walser, A. E. Mark, W. F. van Gunsteren, M. Lauterbach, and G. Wipff, "The effect of force-field parameters on properties of liquids: Parametrization of a simple three-site model for methanol," *J. Chem. Phys.*, vol. 112, no. 23, pp. 10450–10459, 2000.

[128] S. Weerasinghe and P. E. Smith, "A Kirkwood-Buff derived force field for methanol and aqueous methanol solutions," *J. Phys. Chem. B*, vol. 109, no. 31, pp. 15080–15086, 2005.

[129] I. G. Tironi and W. F. van Gunsteren, "A molecular-dynamics simulation study of chloroform," *Mol. Phys.*, vol. 83, no. 2, pp. 381–403, 1994.

[130] R. W. Hockney, "The potential calculation and some applications," *Methods Comput. Phys.*, vol. 9, pp. 136–211, 1970.

[131] H. J. C. Berendsen, J. P. M. Postma, W. F. van Gunsteren, A. Di Nola, and J. R. Haak, "Molecular-dynamics with coupling to an external bath," *J. Chem. Phys.*, vol. 81, no. 8, pp. 3684–3690, 1984.

[132] J.-P. Ryckaert, G. Ciccotti, and H. Berendsen, "Numerical integration of the cartesian equations of motion of a system with constraints: Molecular dynamics of n-alkanes," *J. Comput. Phys.*, vol. 23, pp. 327–341, 1977.

[133] I. G. Tironi, R. Sperb, P. E. Smith, and W. F. van Gunsteren, "A generalized reaction field method for molecular dynamics simulations," *J. Chem. Phys.*, vol. 102, pp. 5451–5495, 1995.

[134] T. N. Heinz, W. F. van Gunsteren, and P. H. Hunenberger, "Comparison of four methods to compute the dielectric permittivity of liquids from molecular dynamics simulations," *J. Chem. Phys.*, vol. 115, no. 3, pp. 1125–1136, 2001.

[135] U. Singh and P. Kollman, "An approach to computing electrostatic charges for molecules," *J. Comput. Chem.*, vol. 5, no. 2, pp. 129–145, 1984.

[136] F. de Proft, F. Tielens, and P. Geerlings, "Performance and basis set dependence of density functional theory dipole and quadrupole moments," *J. Molec. Struc. (Theochem.)*, vol. 506, no. 1–3, pp. 1 – 8, 2000.

[137] R. D. Johnson III, ed., *NIST Standard Reference Database, number 101, release 15b*. National Institute of Standards and Technology, August 2011.

[138] D. P. Geerke and W. F. van Gunsteren, "On the calculation of atomic forces in classical simulation using the charge-on-spring method to explicitly treat electronic polarization," *J. Chem. Theory Comput.*, vol. 3, no. 6, pp. 2128–2137, 2007.

[139] W. R. P. Scott, P. H. Hunenberger, I. G. Tironi, A. E. Mark, S. R. Billeter, J. Fennen, A. E. Torda, T. Huber, P. Kruger, and W. F. van Gunsteren,

"The GROMOS biomolecular simulation program package," *J. Phys. Chem. A*, vol. 103, no. 19, pp. 3596–3607, 1999.

[140] Z. Lin, A. Kunz, and W. F. van Gunsteren, "A one-site polarizable model for liquid chloroform: COS/C," *Mol. Phys.*, vol. 108, no. 13, pp. 1749–1757, 2010.

[141] A. Glättli, X. Daura, and W. F. van Gunsteren, "Derivation of an improved simple point charge model for liquid water: SPC/A and SPC/L," *J. Chem. Phys.*, vol. 116, no. 22, pp. 9811–9828, 2002.

[142] T. Yamaguchi, K. Hidaka, and A. Soper, "The structure of liquid methanol revisited: A neutron diffraction experiment at -80 degrees C and +25 degrees C," *Mol. Phys.*, vol. 96, no. 8, pp. 1159–1168, 1999.

[143] T. Yamaguchi, K. Hidaka, and A. Soper, "The structure of liquid methanol revisited: A neutron diffraction experiment at -80 degrees C and +25 degrees C," *Mol. Phys.*, vol. 97, no. 4, pp. 603–605, 1999.

[144] R. F. Lama and C. Y. Lu, "Excess thermodynamic properties of aqueous alcohol solutions," *J. Chem. Eng. Data*, vol. 10, no. 3, pp. 216–219, 1965.

[145] B. Guillot, "A reappraisal of what we have learnt during three decades of computer simulations on water," *J. Mol Liq.*, vol. 101, no. 1-3, pp. 219–260, 2002.

[146] I. V. Vorobyov, V. M. Anisimov, and A. D. MacKerell, "Polarizable empirical force field for alkanes based on the classical Drude oscillator model," *J. Phys. Chem. B*, vol. 109, no. 40, pp. 18988–18999, 2005.

[147] N. Foloppe and A. D. MacKerell, "All-atom empirical force field for nucleic acids: I. parameter optimization based on small molecule and condensed phase macromolecular target data," *J. Comput. Chem.*, vol. 21, no. 2, pp. 86–104, 2000.

[148] S. Z. Mikhail and W. R. Kimel, "Densities and viscosities of methanol-water mixtures.," *J. Chem. Eng. Data*, vol. 6, no. 4, pp. 533–537, 1961.

[149] A. L. L. McClellan, *Tables of experimental dipole moments.* Rahara enterprise: El Cerrito, USA, 1989.

[150] R. L. Hurle, A. J. Easteal, and L. A. Woolf, "Self-diffusion in monohydric alcohols under pressure. methanol, methan(2h)ol and ethanol," *J. Chem. Soc., Faraday Trans. 1*, vol. 81, pp. 769–779, 1985.

[151] A. R. Katritzky, A. A. Oliferenko, P. V. Oliferenko, R. Petrukhin, D. B. Tatham, U. Maran, A. Lomaka, and W. E. Acree, "A general treatment of solubility. 1. The QSPR correlation of solvation free energies of single solutes in series of solvents," *J. Chem. Inf. Comp. Sc.*, vol. 43, no. 6, pp. 1794–1805, 2003.

[152] J. M. Stout and C. E. Dykstra, "Static dipole polarizabilities of organic molecules. ab initio calculations and a predictive model," *J. Am. Chem. Soc.*, vol. 117, no. 18, pp. 5127–5132, 1995.

[153] W. Xie and J. Gao, "Design of a next generation force field: the X-POL potential," *J. Chem. Theory Comput.*, vol. 3, no. 6, pp. 1890–1900, 2007.

[154] N. Gresh, G. A. Cisneros, T. A. Darden, and J.-P. Piquemal, "Anisotropic, polarizable molecular mechanics studies of inter- and intramolecular interactions and ligandmacromolecule complexes. a bottom-up strategy," *J.*

Chem. Theory Comput., vol. 3, no. 6, pp. 1960–1986, 2007.

[155] A. Warshel, M. Kato, and A. V. Pisliakov, "Polarizable force fields: history, test cases, and prospects," *J. Chem. Theory Comput.*, vol. 3, no. 6, pp. 2034–2045, 2007.

[156] P. Cieplak, F.-Y. Dupradeau, Y. Duan, and J. Wang, "Polarization effects in molecular mechanical force fields," *J. Phys. Cond. Mat.*, vol. 21, no. 33, p. 333102, 2009.

[157] X. Zhu, P. E. M. Lopes, and A. D. MacKerell, "Recent developments and applications of the CHARMM force fields," *Wiley Interdiscip. Rev. Comput. Mol. Sci.*, vol. 2, no. 1, pp. 167–185, 2012.

[158] S. Ou, T. R. Lucas, Y. Zhong, B. A. Bauer, Y. Hu, and S. Patel, "Free energetics and the role of water in the permeation of methyl guanidinium across the bilayer–water interface: Insights from molecular dynamics simulations using charge equilibration potentials," *J. Phys. Chem. B*, vol. 117, no. 13, pp. 3578–3592, 2013.

[159] G. A. Kaminski, H. A. Stern, B. J. Berne, and R. A. Friesner, "Development of an accurate and robust polarizable molecular mechanics force field from ab initio quantum chemistry," *J. Phys. Chem. A*, vol. 108, no. 4, pp. 621–627, 2004.

[160] J. R. Maple, Y. Cao, W. Damm, T. A. Halgren, G. A. Kaminski, L. Y. Zhang, and R. A. Friesner, "A polarizable force field and continuum solvation methodology for modeling of proteinligand interactions," *J. Chem. Theory Comput.*, vol. 1, no. 4, pp. 694–715, 2005.

[161] J. W. Ponder, C. Wu, P. Ren, V. S. Pande, J. D. Chodera, M. J. Schnieders, I. Haque, D. L. Mobley, D. S. Lambrecht, R. A. DiStasio, M. Head-Gordon, G. N. I. Clark, M. E. Johnson, and T. Head-Gordon, "Current status of the AMOEBA polarizable force field," *J. Phys. Chem. B*, vol. 114, no. 8, pp. 2549–2564, 2010.

[162] Y. Zhong and S. Patel, "Nonadditive empirical force fields for short-chain linear alcohols: Methanol to butanol. hydration free energetics and kirkwoodbuff analysis using charge equilibration models," *J. Phys. Chem. B*, vol. 114, no. 34, pp. 11076–11092, 2010.

[163] E. Wernersson and P. Jungwirth, "Effect of water polarizability on the properties of solutions of polyvalent ions: Simulations of aqueous sodium sulfate with different force fields," *J. Chem. Theory Comput.*, vol. 6, no. 10, pp. 3233–3240, 2010.

[164] C. M. Baker, V. M. Anisimov, and A. D. MacKerell, "Development of CHARMM polarizable force field for nucleic acid bases based on the classical Drude oscillator model," *J. Phys. Chem. B*, vol. 115, no. 3, pp. 580–596, 2011.

[165] Y. Shi, Z. Xia, J. Zhang, R. Best, C. Wu, J. W. Ponder, and P. Ren, "Polarizable atomic multipole-based AMOEBA force field for proteins," *J. Chem. Theory Comput.*, vol. 9, no. 9, pp. 4046–4063, 2013.

[166] O. M. Szklarczyk, S. J. Bachmann, and W. F. van Gunsteren, "A polarizable empirical force field for molecular dynamics simulation of liquid hydrocarbons," *J. Comput. Chem.*, vol. 35, no. 10, pp. 789–801, 2014.

[167] C. R. Vosmeer, A. S. Rustenburg, J. E. Rice, H. W. Horn, W. C. Swope, and D. P. Geerke, "QM/MM-based fitting of atomic polarizabilities for use in condensed-phase biomolecular simulation," *J. Chem. Theory Comput.*, vol. 8, no. 10, pp. 3839–3853, 2012.

[168] P. Söderhjelm, A. Öhrn, U. Ryde, and G. Karlström, "Accuracy of typical approximations in classical models of intermolecular polarization," *J. Chem. Phys.*, vol. 128, no. 1, p. 014102, 2008.

[169] G. Maroulis, "Hyperpolarizability of H2O revisited: accurate estimate of the basis set limit and the size of electron correlation effects," *Chem. Phys. Lett.*, vol. 289, no. 3–4, pp. 403–411, 1998.

[170] Y. S. Badyal, M. L. Saboungi, D. L. Price, S. D. Shastri, D. R. Haeffner, and A. K. Soper, "Electron distribution in water," *J. Chem. Phys.*, vol. 112, no. 21, pp. 9206–9208, 2000.

[171] P. L. Silvestrelli and M. Parrinello, "Water molecule dipole in the gas and in the liquid phase," *Phys. Rev. Lett.*, vol. 82, pp. 3308–3311, 1999.

[172] D. S. Cerutti, J. E. Rice, W. C. Swope, and D. A. Case, "Derivation of fixed partial charges for amino acids accommodating a specific water model and implicit polarization," *J. Phys. Chem. B*, vol. 117, no. 8, pp. 2328–2338, 2013.

[173] T. A. Wesolowski and A. Warshel, "Frozen density functional approach for ab initio calculations of solvated molecules," *J. Phys. Chem.*, vol. 97, no. 30, pp. 8050–8053, 1993.

[174] J. Neugebauer, C. R. Jacob, T. A. Wesolowski, and E. J. Baerends, "An explicit quantum chemical method for modeling large solvation shells applied to aminocoumarin c151," *J. Phys. Chem. A*, vol. 109, no. 34, pp. 7805–7814, 2005.

[175] C. R. Jacob, J. Neugebauer, L. Jensen, and L. Visscher, "Comparison of frozen-density embedding and discrete reaction field solvent models for molecular properties," *Phys. Chem. Chem. Phys.*, vol. 8, pp. 2349–2359, 2006.

[176] C. Fonseca Guerra, J. G. Snijders, G. te Velde, and E. J. Baerends, "Towards an order-N DFT method," *Theor. Chem. Acc*, vol. 99, no. 6, pp. 391–403, 1998.

[177] G. te Velde, F. M. Bickelhaupt, E. J. Baerends, C. Fonseca Guerra, S. J. A. van Gisbergen, J. G. Snijders, and T. Ziegler, "Chemistry with ADF," *J. Comput. Chem.*, vol. 22, no. 9, pp. 931–967, 2001.

[178] E. van Lenthe and E. J. Baerends, "Optimized slater-type basis sets for the elements 1–118," *J. Comput. Chem.*, vol. 24, no. 9, pp. 1142–1156, 2003.

[179] W. L. Jorgensen, J. Chandrasekhar, J. D. Madura, R. W. Impey, and M. L. Klein, "Comparison of simple potential functions for simulating liquid water," *J. Chem. Phys.*, vol. 79, no. 2, pp. 926–935, 1983.

[180] C. C. Pye, T. Ziegler, E. van Lenthe, and J. N. Louwen, "An implementation of the conductor-like screening model of solvation within the amsterdam density functional package — part ii. cosmo for real solvents1," *Can. J. Chem*, vol. 87, no. 7, pp. 790–797, 2009.

[181] C. R. Jacob, J. Neugebauer, and L. Visscher, "A flexible implementation of frozen-density embedding for use in multilevel simulations," *J. Comput. Chem.*, vol. 29, no. 6, pp. 1011–1018, 2008.

[182] C. R. Jacob, S. M. Beyhan, R. E. Bulo, A. S. P. Gomes, A. W. Götz, K. Kiewisch, J. Sikkema, and L. Visscher, "PyADF — A scripting framework for multiscale quantum chemistry," *J. Comput. Chem.*, vol. 32, no. 10, pp. 2328–2338, 2011.

[183] A. Lembarki and H. Chermette, "Obtaining a gradient-corrected kinetic-energy functional from the Perdew-Wang exchange functional," *Phys. Rev. A*, vol. 50, pp. 5328–5331, 1994.

[184] T. A. Wesolowski, H. Chermette, and J. Weber, "Accuracy of approximate kinetic energy functionals in the model of Kohn–Sham equations with constrained electron density: The FHNCH complex as a test case," *J. Chem. Phys.*, vol. 105, no. 20, pp. 9182–9190, 1996.

[185] M. Weingarth, E. A. van der Cruijsen, J. Ostmeyer, S. Lievestro, B. Roux, and M. Baldus, "Quantitative analysis of the water occupancy around the selectivity filter of a K+ channel in different gating modes," *J. Am. Chem. Soc*, vol. 136, no. 5, pp. 2000–2007, 2014.

[186] M. Weingarth, A. Prokofyev, E. A. van der Cruijsen, D. Nand, A. M. Bonvin, O. Pongs, and M. Baldus, "Structural determinants of specific lipid binding to potassium channels," *J. Am. Chem. Soc.*, vol. 135, no. 10, pp. 3983–3988, 2013.

[187] B. A. Horta, P. F. Fuchs, W. F. van Gunsteren, and P. H. Hünenberger, "New interaction parameters for oxygen compounds in the GROMOS force field: improved pure-liquid and solvation properties for alcohols, ethers, aldehydes, ketones, carboxylic acids, and esters," *J. Chem. Theory Comput.*, vol. 7, no. 4, pp. 1016–1031, 2011.

[188] D. L. Mobley, É. Dumont, J. D. Chodera, and K. A. Dill, "Comparison of charge models for fixed-charge force fields: small-molecule hydration free energies in explicit solvent," *J. Phys. Chem. B*, vol. 111, no. 9, pp. 2242–2254, 2007.

[189] J. Huang, P. E. M. Lopes, B. Roux, and A. D. MacKerell, "Recent advances in polarizable force fields for macromolecules: Microsecond simulations of proteins using the classical Drude oscillator model," *J. Phys. Chem. Lett.*, vol. 5, no. 18, pp. 3144–3150, 2014.

[190] C. R. Vosmeer, K. Kiewisch, K. Keijzer, L. Visscher, and D. P. Geerke, "A comparison between QM/MM and QM/QM based fitting of condensed-phase atomic polarizabilities," *Phys. Chem. Chem. Phys.*, vol. 16, pp. 17857–17862, 2014.

[191] C. Wohlfahrt, "2 pure liquids: Data," in *Static Dielectric Constants of Pure Liquids and Binary Liquid Mixtures*, pp. 5–228, Springer, 1991.

[192] A. P. Eichenberger, J. R. Allison, J. Dolenc, D. P. Geerke, B. A. C. Horta, K. Meier, C. Oostenbrink, N. Schmid, D. Steiner, D. Wang, and W. F. van Gunsteren, "GROMOS++ software for the analysis of biomolecular simulation trajectories," *J. Chem. Theory Comput.*, vol. 7, no. 10, pp. 3379–3390, 2011.

[193] D. L. Beveridge and F. DiCapua, "Free energy via molecular simulation: applications to chemical and biomolecular systems," *Ann. Rev. Biophys*, vol. 18, no. 1, pp. 431–492, 1989.
[194] M. Neumann, "Dipole moment fluctuation formulas in computer simulations of polar systems," *Mol. Phys.*, vol. 50, no. 4, pp. 841–858, 1983.
[195] J. A. Riddick, W. B. Bunger, and T. K. Sakano, *Organic solvents: physical properties and methods of purification*. John Wiley and Sons, New York, NY, 1986.
[196] G. D. Hawkins, C. J. Cramer, and D. G. Truhlar, "Universal quantum mechanical model for solvation free energies based on gas-phase geometries," *J. Phys. Chem. B*, vol. 102, no. 17, pp. 3257–3271, 1998.
[197] J. T. Partington, R. Hudson, and K. Bagnall, "Self-diffusion of aliphatic alcohols," *Nature*, vol. 169, pp. 583–584, 1952.
[198] N. Karger, T. Vardag, and H.-D. Lüdemann, "Temperature dependence of self-diffusion in compressed monohydric alcohols," *J. Chem. Phys.*, vol. 93, no. 5, pp. 3437–3444, 1990.
[199] Y.-X. Yu and G.-H. Gao, "Study on self-diffusion in water, alcohols and hydrogen fluoride by the statistical associating fluid theory," *Fluid phase equilib.*, vol. 179, no. 1, pp. 165–179, 2001.
[200] S. Meckl and M. Zeidler, "Self-diffusion measurements of ethanol and propanol," *Mol. Phys.*, vol. 63, no. 1, pp. 85–95, 1988.
[201] S. J. Weiner, P. A. Kollman, D. A. Case, U. C. Singh, C. Ghio, G. Alagona, S. Profeta, and P. Weiner, "A new force field for molecular mechanical simulation of nucleic acids and proteins," *J. Am. Chem. Soc*, vol. 106, no. 3, pp. 765–784, 1984.
[202] W. F. van Gunsteren, X. Daura, and A. E. Mark, "GROMOS force field," *Encyclopedia of computational chemistry*, 1998.
[203] J. Wang, W. Wang, P. A. Kollman, and D. A. Case, "Antechamber: an accessory software package for molecular mechanical calculations," *J. Am. Chem. Soc*, vol. 222, p. U403, 2001.
[204] V. Zoete, M. A. Cuendet, A. Grosdidier, and O. Michielin, "Swissparam: A fast force field generation tool for small organic molecules," *J. Comput. Chem.*, vol. 32, no. 11, pp. 2359–2368, 2011.
[205] K. B. Koziara, M. Stroet, A. K. Malde, and A. E. Mark, "Testing and validation of the Automated Topology Builder (ATB) version 2.0: prediction of hydration free enthalpies," *J. Comput. Aided Mol. Des.*, vol. 28, no. 3, pp. 221–233, 2014.
[206] M. R. Shirts, J. W. Pitera, W. C. Swope, and V. S. Pande, "Extremely precise free energy calculations of amino acid side chain analogs: Comparison of common molecular mechanics force fields for proteins," *J. Chem. Phys.*, vol. 119, no. 11, pp. 5740–5761, 2003.
[207] J. L. MacCallum and D. P. Tieleman, "Calculation of the water–cyclohexane transfer free energies of neutral amino acid side-chain analogs using the opls all-atom force field," *J. Comput. Chem.*, vol. 24, no. 15, pp. 1930–1935, 2003.
[208] H. Liu, A. E. Mark, and W. F. van Gunsteren, "Estimating the relative

free energy of different molecular states with respect to a single reference state," *J. Phys. Chem.*, vol. 100, no. 22, pp. 9485–9494, 1996.

[209] R. Eisenschitz and F. London, "Über das verhältnis der van der waalsschen kräfte zu den homöopolaren bindungskräften," *Z. Phys.*, vol. 60, no. 7-8, pp. 491–527, 1930.

[210] F. London, "Zur theorie und systematik der molekularkräfte," *Z. Phys.*, vol. 63, no. 3-4, pp. 245–279, 1930.

[211] F. London, "The general theory of molecular forces," *Transactions of the Faraday Society*, vol. 33, no. 0, pp. 8b–26, 1937.

[212] J. C. Slater and J. G. Kirkwood, "The van der Waals forces in gases," *Phys. Rev.*, vol. 37, pp. 682–697, 1931.

[213] A. D. Buckingham, P. W. Fowler, and J. M. Hutson, "Theoretical studies of van der Waals molecules and intermolecular forces," *Chem. Rev*, vol. 88, no. 6, pp. 963–988, 1988.

[214] T. A. Halgren, "Representation of van der Waals (vdW) interactions in molecular mechanics force fields: Potential form, combination rules, and vdW parameters," *J. Am. Chem. Soc.*, vol. 114, pp. 7827–7843, 1992.

[215] T. C. Beutler, A. E. Mark, R. C. van Schaik, P. R. Gerber, and W. F. van Gunsteren, "Avoiding singularities and numerical instabilities in free energy calculations based on molecular simulations," *Chem. Phys. Lett.*, vol. 222, no. 6, pp. 529–539, 1994.

[216] M. Zacharias, T. Straatsma, and J. McCammon, "Separation-shifted scaling, a new scaling method for Lennard-Jones interactions in thermodynamic integration," *J. Chem. Phys.*, vol. 100, no. 12, pp. 9025–9031, 1994.

[217] J. D. Chodera, D. L. Mobley, M. R. Shirts, R. W. Dixon, K. Branson, and V. S. Pande, "Alchemical free energy methods for drug discovery: progress and challenges," *Curr. Opin. Struct. Biol.*, vol. 21, no. 2, pp. 150 – 160, 2011.

[218] M. D. Parenti and G. Rastelli, "Advances and applications of binding affinity prediction methods in drug discovery," *Biotechnol. Adv.*, vol. 30, no. 1, pp. 244–250, 2012.

[219] C. de Graaf, C. Oostenbrink, P. H. J. Keizers, B. M. A. van Vugt-Lussenburg, J. N. M. Commandeur, and N. P. E. Vermeulen, "Free energies of binding of R- and S-propranolol to wild-type and F483A mutant cytochrome P450 2D6 from molecular dynamics simulations," *Eur. Biophys. J.*, vol. 36, no. 6, pp. 589–599, 2007.

[220] E. Stjernschantz, N. P. E. Vermeulen, and C. Oostenbrink, "Computational prediction of drug binding and rationalisation of selectivity towards cytochromes P450," *Expert Opin. Drug Metab. Tox.*, vol. 4, no. 5, pp. 513–527, 2008.

[221] J. Kirchmair, M. J. Williamson, J. D. Tyzack, L. Tan, P. J. Bond, A. Bender, and R. C. Glen, "Computational prediction of metabolism: Sites, products, SAR, P450 enzyme dynamics, and mechanisms," *J. Chem. Inf. Model.*, vol. 52, no. 3, pp. 617–648, 2012.

[222] P. Ortiz de Montellano, *Cytochrome P450: Structure, Mechanism, and Biochemistry, 3rd ed.* Kluwer Academic/Plenum Publishers, New York,

2005.

[223] G. Rastelli, A. D. Rio, G. Degliesposti, and M. Sgobba, "Fast and accurate predictions of binding free energies using MM-PBSA and MM-GBSA," *J. Comput. Chem.*, vol. 31, no. 4, pp. 797–810, 2010.

[224] G. Klebe, "Virtual ligand screening: strategies, perspectives and limitations," *Drug Discov. Today*, vol. 11, no. 13/14, pp. 580–594, 2006.

[225] C. D. Christ, A. E. Mark, and W. F. van Gunsteren, "Basic ingredients of free energy calculations: A review," *J. Comput. Chem.*, vol. 31, no. 8, pp. 1569–1582, 2010.

[226] A. de Ruiter and C. Oostenbrink, "Free energy calculations of protein–ligand interactions," *Curr. Opin. Chem. Biol.*, vol. 15, no. 4, pp. 547–552, 2011.

[227] F. Guengerich, "Cytochrome P450s and other enzymes in drug metabolism and toxicity," *AAPS J.*, vol. 8, pp. E101–E111, 2006.

[228] J. Hritz and C. Oostenbrink, "Efficient free energy calculations for compounds with multiple stable conformations separated by high energy barriers," *J. Phys. Chem. B*, vol. 113, no. 38, pp. 12711–12720, 2009.

[229] G. Rastelli, G. Degliesposti, A. Del Rio, and M. Sgobba, "Binding estimation after refinement, a new automated procedure for the refinement and rescoring of docked ligands in virtual screening," *Chem. Biol. Drug Des.*, vol. 73, no. 3, pp. 283–286, 2009.

[230] J. Hritz, A. de Ruiter, and C. Oostenbrink, "Impact of plasticity and flexibility on docking results for Cytochrome P450 2D6: A combined approach of molecular dynamics and ligand docking," *J. Med. Chem.*, vol. 51, no. 23, pp. 7469–7477, 2008.

[231] P. Vasanthanathan, L. Olsen, F. S. Jørgensen, N. P. E. Vermeulen, and C. Oostenbrink, "Computational prediction of binding affinity for CYP1A2-ligand complexes using empirical free energy calculations," *Drug Metab. Dispos.*, vol. 38, no. 8, pp. 1347–1354, 2010.

[232] E. Stjernschantz, J. Marelius, C. Medina, M. Jacobsson, N. P. E. Vermeulen, and C. Oostenbrink, "Are automated molecular dynamics simulations and binding free energy calculations realistic tools in lead optimization? an evaluation of the linear interaction energy (LIE) method," *J. Chem. Inf. Model.*, vol. 46, no. 5, pp. 1972–1983, 2006.

[233] X. Daura, W. F. van Gunsteren, and A. E. Mark, "Folding-unfolding thermodynamics of a β-heptapeptide from equilibrium simulations," *Prot. Struct. Funct. Bioinf.*, vol. 34, no. 3, pp. 269–280, 1999.

[234] B. Keller, X. Daura, and W. F. Van Gunsteren, "Comparing geometric and kinetic cluster algorithms for molecular simulation data," *J. Chem. Phys.*, vol. 132, no. 7, p. 074110, 2010.

[235] J. Wang, W. Wang, P. A. Kollman, and D. A. Case, "Automatic atom type and bond type perception in molecular mechanical calculations," *J. Molec. Graph. Model.*, vol. 25, no. 2, pp. 247–260, 2006.

[236] K. Vanommeslaeghe and A. D. MacKerell, "Automation of the CHARMM General Force Field (CGenFF) I: Bond Perception and Atom Typing," *J. Chem. Inf. Model.*, vol. 52, no. 12, pp. 3144–3154, 2012.

[237] K. Vanommeslaeghe, E. P. Raman, and A. D. MacKerell, "Automation of the CHARMM General Force Field (CGenFF) II: Assignment of Bonded Parameters and Partial Atomic Charges," *J. Chem. Inf. Model.*, vol. 52, no. 12, pp. 3155–3168, 2012.

[238] R. J. Vaz, A. Nayeem, K. Santone, G. Chandrasena, and A. V. Gavai, "A 3D-QSAR model for CYP2D6 inhibition in the aryloxypropanolamine series," *Bioorg. Med. Chem. Let.*, vol. 15, no. 17, pp. 3816–3820, 2005.

[239] C. Yung-Chi and W. H. Prusoff, "Relationship between the inhibition constant (KI) and the concentration of inhibitor which causes 50 per cent inhibition (IC50) of an enzymatic reaction," *Biochem. Pharmacol.*, vol. 22, no. 23, pp. 3099–3108, 1973.

[240] "http://www.caliperls.com/products/cyp2d6-h.htm," 10 2013.

[241] M. Eldridge, C. Murray, T. Auton, G. Paolini, and R. Mee, "Empirical scoring functions: I. the development of a fast empirical scoring function to estimate the binding affinity of ligands in receptor complexes," *J. Comput. Aided Mol. Des.*, vol. 11, pp. 425–445, 1997.

[242] G. Jones, P. Willett, R. C. Glen, A. R. Leach, and R. Taylor, "Development and validation of a genetic algorithm for flexible docking," *J. Mol. Biol.*, vol. 267, pp. 727–748, 1997.

[243] R. D. Lins and P. H. Hünenberger, "A new GROMOS force field for hexopyranose-based carbohydrates," *J. Comput. Chem.*, vol. 26, no. 13, pp. 1400–1412, 2005.

[244] C. R. Vosmeer, R. Pool, M. F. van Stee, L. Perić-Hassler, N. P. E. Vermeulen, and D. P. Geerke, "Towards automated binding affinity prediction using an iterative Linear Interaction Energy approach," *Int. J. Mol. Sci.*, vol. 15, no. 1, pp. 798–816, 2014.

[245] L. Capoferri, D. P. Geerke, and N. P. E. Vermeulen *manuscript in preparation*, 2014.

[246] O. Korb, T. Stützle, and T. E. Exner, "PLANTS: Application of ant colony optimization to structure-based drug design," in *Ant Colony Optimization and Swarm Intelligence*, pp. 247–258, Springer, 2006.

[247] O. Korb, T. Stutzle, and T. E. Exner, "Empirical scoring functions for advanced protein–ligand docking with PLANTS," *J. Chem. Inf. Model.*, vol. 49, no. 1, pp. 84–96, 2009.

[248] B. Hess, C. Kutzner, D. van der Spoel, and E. Lindahl, "GROMACS 4: Algorithms for highly efficient, load-balanced, and scalable molecular simulation," *J. Chem. Theory Comput.*, vol. 4, no. 3, pp. 435–447, 2008.

[249] K. Shahrokh, A. Orendt, G. S. Yost, and T. E. Cheatham, "Quantum mechanically derived AMBER-compatible heme parameters for various states of the cytochrome P450 catalytic cycle," *J. Chem. Theory Comput.*, vol. 33, no. 2, pp. 119–133, 2012.

[250] A. W. S. da Silva and W. F. Vranken, "ACPYPE-Antechamber python parser interface," *BMC research notes*, vol. 5, no. 1, p. 367, 2012.

[251] V. Hornak, R. Abel, A. Okur, B. Strockbine, A. Roitberg, and C. Simmerling, "Comparison of multiple Amber force fields and development of improved protein backbone parameters," *Proteins: Struct., Funct., Bioinf.*,

vol. 65, no. 3, pp. 712–725, 2006.

[252] T. J. Lane, D. Shukla, K. A. Beauchamp, and V. S. Pande, "To milliseconds and beyond: challenges in the simulation of protein folding," *Curr. Opin. Struct. Biol.*, vol. 23, no. 1, pp. 58 – 65, 2013.

[253] K. Berka, M. Paloncýová, P. Anzenbacher, and M. Otyepka, "Behavior of human Cytochromes P450 on lipid membranes," *J. Phys. Chem. B*, vol. 117, no. 39, pp. 11556–11564, 2013.

[254] D. P. Geerke, S. Thiel, W. Thiel, and W. F. van Gunsteren, "Combined QM/MM molecular dynamics study on a condensed-phase S(N)2 reaction at nitrogen: The effect of explicitly including solvent polarization," *J. Chem. Theory Comput.*, vol. 3, no. 4, pp. 1499–1509, 2007.

[255] V. Chupakhin, G. Marcou, I. Baskin, A. Varnek, and D. Rognan, "Predicting ligand binding modes from neural networks trained on protein–ligand interaction fingerprints," *J. Chem. Inf. Model.*, vol. 53, no. 4, pp. 763–772, 2013.

[256] P. Carriò, M. Pinto, G. Ecker, F. Sanz, and M. Pastor, "Applicability Domain Analysis (ADAN): A robust method for assessing the reliability of drug property predictions," *J. Chem. Inf. Model.*, vol. 54, no. 5, pp. 1500–1511, 2014.